II. REMARKS

A. Status of the Claims

Claims 24-40, 42, 44, 45, and 61 are pending in the application. In the Action, the Examiner held that claims 41 and 43 are withdrawn from consideration, as drawn to non-elected species. Claim 25 has been canceled, claim 24 has been amended in the Amendment contained herein, and claim 62 has been added. No new matter is added by the Amendment and new claim, and support for the Amendment and new claim can be found in the specification and claims as originally filed. Therefore, claims 24, 26-45, and 61-62 are pending. Reentry of claims 41 and 43 in view of the allowability of claim 24 is requested below.

B. The Rejections of Claim 25 Under 35 U.S.C. §§ 101 and 112 are Rendered Moot

The Action rejects claim 25 under 35 U.S.C. § 101 because the claim is said to be directed to non-statutory subject matter. The Action also rejects claim 25 under 35 U.S.C. § 112, second paragraph, because the claim is said to be indefinite due to Applicant allegedly claiming more than one statutory class of invention in the same claim. While Applicant disagrees that claim 25 is directed to non-statutory subject matter and that it is indefinite (as explained in the previous Response dated 6/23/05, which is incorporated herein by reference in its entirety), in the interest of furthering the prosecution of this case, Applicant notes that claim 25 has been canceled in the Amendment contained herein. Therefore, these rejections are rendered moot.

C. Summary of the Primary Issues

Given the mootness of the rejections of claim 25, the primary issues that remain to be resolved in the present application are: (1) the Action's contention that the term "large-area fluorescent excitation" is indefinite, (2) the Action's contention that the Sharonov and Sanchez references inherently disclose a light source that is adapted for use in large-area fluorescent excitation, and (3) whether Schmidt teaches a control unit adapted to coordinate and synchronize

illumination times and lateral movement. As explained below, the term "large-area fluorescent excitation" has the same meaning to a person of ordinary skill in the art as the term "wide-field illumination" and is therefore not indefinite. Furthermore, the Sharonov and Sanchez references do not inherently disclose a light source that is configured for use in large-area fluorescent excitation, and therefore they do anticipate the present claims. Applicant's positions on these primary issues are fully supported by the Supplemental Declaration of Dr. Max Sonnleitner that is attached as Appendix A to this Submission. In addition, Schmidt fails to disclose a control unit adapted to coordinate and synchronize illumination times and lateral movement.

D. The Indefiniteness Rejections are Overcome

The Action rejects claims 24-40, 42, 45, and 61 under 35 U.S.C. § 112, second paragraph, as being indefinite and/or unclear. The Action maintains that "the term 'large-area' [in claim 24] is a relative term, which renders the claim indefinite and/or unclear." The Action, p. 5. The Action also rejects these claims because the phrase "wherein the arrangement is adapted to visualize movements of molecules . . . by using the single dye tracing (SDT) method" is said to be vague and indefinite. The Action, p. 37. Applicant respectfully traverses these rejections.

1. *The term "large-area fluorescent excitation" is not indefinite.*

In the previous Response, Applicant relied upon the declaration of Dr. Max Sonnleitner (attached as Appendix A to that Response) to establish that the term "large area fluorescent excitation" is not indefinite. As set forth in the Sonnleitner Declaration, the term "large area fluorescent excitation" would be well-understood by a hypothetical person possessing the ordinary level of skill in the pertinent art. Despite the Action's statements to the contrary, the Sonnleitner Declaration is sufficient to establish that the term in question is not indefinite.

The Action asserts that if the terms "large-area fluorescent excitation" and "wide-field illumination" possess the exact same meaning as stated by Dr. Sonnleitner, then Applicant should have no trouble documenting this assertion or pointing to pertinent portions of the specification that support this conclusion. The Action, p. 7. The Action further contends that Applicant has failed to provide a reference that sets forth a definition for "large-area fluorescent excitation." *Id.*

As an initial matter, Applicant notes that the Action's wholesale dismissal of Dr. Sonnleitner's declaration and the Action's requirement that Applicant point to additional evidence go far beyond what is required by U.S. law. The test for definiteness under 35 U.S.C. § 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576 (Fed. Cir. 1986). To properly controvert declaratory evidence submitted by the Applicant, "the examiner must specifically explain why the evidence is insufficient." MPEP § 716.01. Merely stating that Dr. Sonnleitner's statements are "unsupported" is not a specific explanation of why the evidence is insufficient. As a person of ordinary skill in the art, Dr. Sonnleitner is qualified to establish whether a term would be understood by those of skill in the art. There is no requirement that he "support" such a statement—the fact that he is a person of skill in the art is itself adequate "support" for the statement. If the Examiner is of the opinion that Dr. Sonnleitner's sworn statement is untrue, the onus is on the Examiner to put forth his own evidence in support of that opinion.

Despite the Action's reliance on an improper standard in dismissing Applicant's declaratory evidence, in the interest of furthering the prosecution in this case, Applicant is

willing to provide further evidence herein to establish that "large-area fluorescent excitation" is not indefinite.

The Action's characterization of "large-area" as a relative term is incorrect. In the context of the present specification and claims, the term "large-area" is used to distinguish the light source of the present arrangement from the light source used in confocal microscopy (in which a "small" area is illuminated). As would be easily understood by one of skill in the art, the terms "large" and "small" in this context are used to distinguish two different techniques (i.e., non-confocal microscopy and confocal microscopy). That the term "large-area" is being used to distinguish the present arrangement from one involving confocal microscopy (in which illumination is performed pixel-wise, i.e., on a spot) is evident in the specification at, for example, page 27.

As the Sonnleitner Declaration establishes, one of ordinary skill in the art would understand what is meant by the term "large-area fluorescent excitation" in this context (i.e., that it is synonymous with "wide-field illumination"). Submitted herewith is a supplemental declaration from Dr. Sonnleitner (attached as Appendix A) ("Supplemental Sonnleitner Declaration"). The Supplemental Sonnleitner Declaration establishes that his statement in his initial declaration that a person of ordinary skill in the art would understand the meaning of the term "large-area fluorescent excitation" in the context of the specification and claims (i.e., that it is synonymous with "wide-field illumination") is supported by the following evidence:

- the article "Ultra-Sensitive Fluorescence Reader for Bioanalysis" by Hesse, *et al.*, Cur.Pharma.Biotechnol. 5 (2004):309-319 ("Hesse-1") (attached as Appendix B), which makes frequent reference to illuminating "large sample areas" (p. 310, col. 1) during a process referred to as "wide field illumination" (p. 311, Fig. 1B and description);
- the article "Single-Molecule Reader for Proteomics and Genomics" by Hesse, *et al.*, J. Chromatography B 782 (2002):127-135 ("Hesse-2") (attached as Appendix C), which explicitly differentiates confocal microscopy (p. 128, col.

2) from an approach in which "large sample areas are illuminated" (p. 129, col. 1), a process referred to as "large area screening" (Abstract);

- the article "High-throughput scanning with single molecule sensitivity" by Sonnleitner, *et al.*, Proc. SPIE, 5699 (2005):202-210 ("Sonnleitner-1") (attached as Appendix D), which explicitly differentiates (in Section 2.1) confocal scanning from a scanning technique that involves "large areas," which is referred to as "wide-field illumination"; and

- the fact that the German word "großflächig," which was used in the original, un-translated priority document, may be translated in English as either "large-area" or "wide-field."

2. *The phrase "wherein the arrangement is adapted to visualize movements of molecules . . . by using the single dye tracing (SDT) method" is not indefinite.*

As an initial matter, Applicant notes that this limitation has been removed from independent claim 24 and now appears in dependent claim 62. According to the Action, this limitation is indefinite because the recitation of a use "results in an improper definition of a process." The Action, p. 37. This is an improper statement of the law. A recitation of a use does not automatically render a claim indefinite. *See*, *Ex Parte Porter*, 25 U.S.P.Q.2d 1144 (Bd. Pat. App. & Inter. 1992) (Board held that a claim which recited the step of "utilizing" was not indefinite); *see also* MPEP § 2173.05(q). The term "by using the single dye tracing (SDT) method" modifies the structural limitation "adapted to visualize movements of molecules." As the SDT technique is discussed in great detail in the specification, a person of skill in the art would understand the claim when the claim is read in light of the specification. *See In re Moore*, 439 F.2d 1232, 1235 (CCPA 1971) ("The definiteness of the language employed must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.").

The Action's reliance on Applicant's previous statements regarding Schmidt does not establish that claim 62 is indefinite. Contrary to the assertions of the Action, Applicant never

stated in the previous Response that "this SDT method does not lead to the currently claimed 'visualization of movements of molecules.'" The Action, p. 38. What Applicant actually said in the previous Response was that Schmidt "does not teach the visualization of movements of molecules, interactions between molecules, and molecular processes **within a three-dimensional biological cell or cells**; it only discloses artificial flat-surface lipids." Response dated 6/23/05, p. 17 (emphasis added). Thus, Applicant never "expressly acknowledged" that SDT methods could not be used to visualize movements of molecules, interactions between molecules, and molecular processes in a sample. To the contrary, Applicant has consistently maintained that SDT methods can be used to visualize movements of molecules, interactions between molecules, and molecular processes in a sample, a fact which is easily understood by a person of ordinary skill in the art.

In view of the above, the rejections to independent claim 24 and its pending dependent claims, claims 26-40, 42, 45, and 61, as being indefinite and/or unclear are overcome and should be withdrawn.

E. The Anticipation Rejections are Overcome

The Action rejects claims 24-28, 30-34, and 61 under 35 U.S.C. § 102(b) as being anticipated by Sharonov, *et al.* ("Sharonov"). The Action rejects claims 24, 26, 27, 30, 32, 34, 35, 37, and 61 as being anticipated by Sanchez, *et al.* ("Sanchez"). Applicant traverses both of these rejections. Neither Sharonov nor Sanchez teaches any of the following three elements of the claims: (1) a light source configured for use in large-area fluorescent excitation, (2) a control unit adapted to coordinate and synchronize illumination times and lateral movement, and (3) an arrangement adapted to visualize movements . . . by using a single dye tracing (SDT) method.

1. *Sharonov and Sanchez do not teach "a light source configured for use in large-area fluorescent excitation."*

According to the Action, "Sharonov . . . disclose[s] an apparatus for confocal spectral imaging analysis . . ., which anticipates claims 24 and 61." The Action, p. 8. Sanchez is also directed solely to confocal microscopy. Sanchez, p. 7019. The fact that Sharonov and Sanchez are directed solely to **confocal** microscopy is precisely the reason that Sharonov and Sanchez do not anticipate the present claims, as confocal microscopy is completely different from the large-area fluorescent excitation technique taught by the present claims. The fact that Sharonov and Sanchez appear to disclose the use of a laser does not amount to an inherent teaching of a light source configured for use in large-area fluorescent excitation (i.e., wide-field illumination). Given the differences in the two techniques, a laser that is configured for use in large-area fluorescent excitation is decidedly different from a laser that is configured for use in confocal microscopy. Supplemental Sonnleitner Declaration (attached as Appendix A), pp. 3-4.

As explained above, in the context of the present specification and claims, the term "large-area fluorescent excitation" is used to distinguish the light source of the present arrangement from the light source used in confocal microscopy (in which a "small" area is illuminated). As would be easily understood by one of skill in the art, the terms "large" and "small" in this context are used to distinguish two different techniques (i.e., non-confocal microscopy and confocal microscopy).

That the term "large-area" is being used to distinguish the present arrangement from one which employs confocal microscopy (in which illumination is performed pixel-wise, i.e., on a spot) is evident in the specification at, for example, page 27. Hesse-2 (attached as Appendix C) explicitly differentiates confocal microscopy (p. 128, col. 2) from an approach in which "large sample areas are illuminated" (p. 129, col. 1), a process referred to as "large area screening"

(Abstract). Similarly, Sonnleitner-1 (attached as Appendix D) explicitly differentiates (in Section 2.1) confocal scanning from a scanning technique that involves "large areas," which is referred to as "wide-field illumination."

As set forth in Sonnleitner-1, confocal scanning is based on scanning a diffraction limited laser focus over the sample. The fluorescence emitted from the sample is imaged onto a point detector. Due to the serial data acquisition, the inspection of large sample areas remains a time-consuming task. In particular, in single molecule detection, although the fluorescence of a dye molecule increases linearly with excitation intensity in the low intensity regime, the fluorescence saturates at a certain excitation intensity. Thus, it is not possible to use high illumination intensities to compensate for short illumination times. For common fluorophores this induces minimum pixel dwell times of ~10 ohms to obtain detectable single molecule signals. For example, scanning an area of 1 cm with single molecule sensitivity with a pixel-size of 320 nm and the minimum dwell time of 10 ohms would take 9.9×10^6 seconds (corresponding to 3.8 months!). This shows that diffraction limited confocal scanning with single molecule sensitivity and sub-micron pixel-resolution cannot be applied to readout large microarrays within reasonable times. To enable readout of microarrays on a minute times scale with this pixel-wise scanning, conventional readers use pixel-resolutions of 5 to 10 μm.

In contrast, the large-area fluorescent excitation (wide-field illumination) technique uses a series of images ("panels") of adjacent regions of the sample using, for example, a white-light lamp for illumination and coverage of large areas. In this technique, sequential images are acquired in order to cover large areas. In practice, the usage of frame-transfer cameras allows for the acceleration of the measurement by synchronous illumination and readout. In single molecule detection this can only be exploited when using high intensity laser sources instead of

white-light lamps to get sufficient excitation intensities. However, proper sample positioning limits the overall readout speed in any sequential recording device. Therefore, inertia of the moving parts requires time-consuming feedback loops for precise stops. A rough estimation for scanning 1 cm yields about 10 hours scanning time.

As should be clear from the above explanation from Sonnleitner-1, crucial for all techniques for single molecule detection is the speed and sensitivity of the readout process, specifically if processes with a movement of single molecules should be determined. Sensitivity, reproducibility, and readout velocity represent the key issues for the readout process. Larger areas in confocal microscopy can only be inspected by serial data acquisition, which is highly time consuming. On the other hand, large-area (wide-field) illumination accelerates the measurement by synchronous illumination and readout. However, using conventional fluorescence microscopes, this technique takes considerable scanning time. Therefore, an advantage of the present invention is that it provides a large-area illumination device which is constructed to allow significantly reduced scanning times, which allows detection of single molecule movements on cells or surfaces in real time. Light sources, such as lasers, that are configured for use in confocal microscopy simply will not work for large-area fluorescent excitation.

Because Sharonov and Sanchez do not teach a light source configured for use in large-area fluorescent excitation, they do not teach or suggest each and every element of the present claims. Thus, the anticipation rejections cannot be maintained and should be withdrawn.

2. *Sharonov and Sanchez do not teach "a control unit adapted to coordinate and synchronize illumination times and lateral movement."*

The control unit of the present claims is adapted to coordinate and synchronize illumination times and lateral movement between the sample holder and the detection analysis

system during use. This control unit allows one to synchronize the lateral movement of the stage in scanning direction with the readout of the camera. Each time a camera line is readout (during which the electrons of a pixel-row on the camera chip are transferred to the next pixel-row), the control unit triggers the stage to move the sample exactly the distance corresponding to the camera pixel size divided by the magnification of the microscope objective. *See* the specification, at pp. 11-12. This means that the electrons generated by the photons emitted by one fluorophore are transported along the camera chip with the same velocity as the fluorophore in the sample that is moved by the stage. *See id.* The control unit drives the stage in a quasi-continuous motion. Therefore, the photons emitted by one fluorophore are integrated on the camera chip. For example, if the camera pixel-size is 6.45 μm (common) and an objective with x100 magnification is used, each trigger from the control unit triggers the stage to move 0.0645 μm.

Neither Sharonov nor Sanchez discloses a control unit adapted to coordinate and synchronize illumination times and lateral movement between a sample holder and a detection and analysis system during use. As acknowledged by the Action, Sharonov merely states, "The scanning of the sample stage and mirrors of the optical scanner and all operations connected with recording of spectra are computer-controlled." The Action, p. 10. A disclosure that scanning operations are "computer-controlled" does not amount to the teaching of a controller adapted to **coordinate** and **synchronize** illumination times and lateral movement. The Action asserts that Sanchez's disclosure that "a modified Nanoscope IIIA controller was used for controlling the scan bed and image acquisition" (The Action, p. 17) amounts to the teaching of a controller adapted to coordinate and synchronize illumination times and lateral movement. The disclosure that a "controller" was used for controlling the scan bed and image acquisition does not amount

to the teaching of a controller adapted to **coordinate** and **synchronize** illumination times and lateral movement.

Because Sharonov and Sanchez do not teach a control unit adapted to coordinate and synchronize illumination times and lateral movement, they do not teach or suggest each and every element of the present claims. Thus, the anticipation rejections cannot be maintained and should be withdrawn.

3. *Sharonov and Sanchez do not teach "wherein the arrangement is adapted to visualize movements of molecules . . . by using a single dye tracing (SDT) method."*

The Action concedes that Sharonov and Sanchez "do not explicitly state that said arrangement has been 'adapted' to visualize movements of molecules . . . by using a single dye tracing (SDT) method." The Action, pp. 10, 17. The Action contends that this limitation is inherently disclosed in each of these references, or in the alternative, this language is "intended use" language and is thus not deserving of patentable weight. The Action, pp. 11, 18. As noted above, this limitation has been removed from independent claim 24 and now appears in dependent claim 62.

The Action's statement that Sharonov inherently discloses use of an SDT method because it discloses the use of a "single dye" such as mitroxantrone is incorrect. As stated in the Sonnleitner Declaration attached to the previous Response, Sharonov teaches nothing about SDT. SDT is a technique that combines molecular recognition by antibodies or ligands with time-resolved fluorescence microscopy of single fluorophors for the study of single biomolecules in physiological environments or in isolation, with information about position, motion, conformational transitions, associations and stoichiometries. Merely disclosing the use of a "single dye" in an experiment does not amount to a teaching of the particular technique known as SDT.

The Action's statement that Sanchez inherently discloses use of an SDT method because it discloses "imaging of single dye molecules" is incorrect. As stated in the Sonnleitner Declaration attached to the previous Response, Sanchez teaches nothing about SDT. Merely disclosing the "imaging of single dye molecules" does not amount to a teaching of the particular technique known as SDT.

The Action does not substantively address the Sonnleitner Declaration's statement that Sharonov and Sanchez to not teach the use of SDT. To properly controvert declaratory evidence submitted by the Applicant, "the examiner must specifically explain why the evidence is insufficient." MPEP § 716.01. Merely stating that Dr. Sonnleitner's statements are "unpersuasive" is not a specific explanation of why the evidence is insufficient. As a person of ordinary skill in the art, Dr. Sonnleitner is qualified to establish whether Sharonov and Sanchez teach the use of SDT.

The Action's "alternative" argument that this limitation does not warrant patentable weight because it represents "intended use" language is meritless. The Action contends that this limitation "only sets forth what the apparatus does . . . rather than what it is." The Action, pp. 11, 19. In the context of the specification and claims, the language "adapted to visualize movements of molecules" sets forth a clear structural limitation for the arrangement.

Because Sharonov and Sanchez do not teach and arrangement that is adapted to visualize movements of molecules . . . by using a single dye tracing (SDT) method, they do not teach or suggest each and every element of present claim 62, and claim 62 is thus allowable.

F. The Obviousness Rejections are Overcome

1. *Claims 24, 26-27, 29-30, 32, 34-35, 37, 44, and 61 are not obvious over Sanchez and Lewis*

The Action rejects claims 24, 26-27, 29-30, 32, 34-35, 37, 44, and 61 under 35 U.S.C. § 103(a) as being obvious over Sanchez in view of Lewis, *et al.* ("Lewis"). According to the Action, Sanchez teaches all of the limitations of claims 24, 26-27, 30, 32, 34-35, 37, and 61, "which anticipates, and, as a result, renders obvious" those claims. The Action concedes that certain limitations of claims 29 and 44 are not taught by Sanchez, but it asserts that the deficient teachings are supplied by Lewis. Applicant traverses.

As explained in detail above, Sanchez does not teach all of the limitations of claim 24, the lone independent claim. Sanchez does not teach (1) a light source configured for use in large-area fluorescent excitation, or (2) a control unit adapted to coordinate and synchronize illumination times and lateral movement. For at least these reasons, a *prima facie* case of obviousness has not been established. *See In re Vaeck*, 947 F.2d 488, (Fed Cir. 1991). The rejection of claims 24, 26-27, 29-30, 32, 34-35, 37, 44, and 61 as obvious over Sanchez and Lewis should therefore be withdrawn.

2. *Claims 24-40, 42, 44-45, and 61 are not obvious over Schmidt, Lewis, Al-Ghoul, and Albertine*

The Action rejects claims 24-40, 42, 44, 45, and 61 under 35 U.S.C. § 103(a) as being over Schmidt, *et al.* ("Schmidt"), Lewis, Al-Ghoul, *et al.* ("Al-Ghoul), and Albertine, *et al.* ("Albertine"). According to the Action, Schmidt teaches all of the limitations of claims 24-28, 30-39, and 45. The Action concedes that certain limitations of claims 29, 35, 40, 42, 44 are not taught by Schmidt, but it asserts that the deficient teachings are supplied by Lewis, Al-Ghoul, and Albertine (the Action does not substantively address which specific references teach the limitations of claim 61). Applicant traverses.

Schmidt does not teach a control unit adapted to coordinate and synchronize illumination times and lateral movement between a sample holder and a detection and analysis system during use. In fact, the Action does not even assert that Schmidt teaches a control unit adapted to coordinate and synchronize illumination times **and lateral movement**, instead merely arguing that Schmidt teaches "a control unit adapted to coordinate and synchronize illumination times." The Action, p. 27. For this reason alone, the Action fails to establish a *prima facie* case of obviousness.

Furthermore, as acknowledged by the Action, Schmidt merely discloses "a CCD camera equipped with a TH512B chip . . . 'provid[ing] trigger pulses for the acousto-optic modulator for repeated illuminations.'" The Action, p. 27. This disclosure does not amount to the teaching of a control unit adapted to coordinate and synchronize illumination times and lateral movement.

The control unit of the present claims allows one to synchronize the lateral movement of the stage in scanning direction with the readout of the camera. Each time a camera line is readout (during which the electrons of a pixel-row on the camera chip are transferred to the next pixel-row), the control unit triggers the stage to move the sample exactly the distance corresponding to the camera pixel size divided by the magnification of the microscope objective. *See* the specification, at pp. 11-12. This means that the electrons generated by the photons emitted by one fluorophore are transported along the camera chip with the same velocity as the fluorophore in the sample that is moved by the stage. *See id.* The control unit drives the stage in a quasi-continuous motion. Therefore, the photons emitted by one fluorophore are integrated on the camera chip. For example, if the camera pixel-size is 6.45 μm (common) and an objective with x100 magnification is used, each trigger from the control unit triggers the stage to move

0.0645 μm. Thus, the control unit of the present claims is completely different from the sequential recording (i.e., "trigger pulse") system of Schmidt.

As explained in detail above, Schmidt does not teach all of the limitations of claim 24, the lone independent claim. For at least this reason, a *prima facie* case of obviousness has not been established. The rejection of claims 24-40, 42, 44, 45, and 61 as obvious over Schmidt in view of Lewis, Albertine, and Al-Ghoul should therefore be withdrawn.

G. Entry of Non-elected Species Is Requested

In view of the foregoing arguments, all the presented claims are in condition of allowance. Thus, all species contained in the dependent claims withdrawn by the examiner (claims 41 and 43) should be reentered into the case and allowed. Applicant respectfully requests that all such dependent claims be considered and allowed.

H. Conclusion

Applicant believes that the foregoing remarks fully respond to all outstanding matters for this application. The present claims are allowable for the following primary reasons:

(1) as established by the Supplemental Sonnleitner Declaration, the term "large-area fluorescent excitation" is not indefinite because it is well-understood by persons of ordinary skill in the art; and

(2) as established by the Supplemental Sonnleitner Declaration, the Sharonov and Sanchez references do not anticipate the present claims at least because they do not disclose a light source that is configured for use in large-area fluorescent excitation; and

(3) the Schmidt reference does not teach a control unit adapted to coordinate and synchronize illumination times and lateral movement between a sample holder and a detection and analysis system during use.

Applicant respectfully requests that the rejections of all claims be withdrawn so they may pass to issuance.